Multiscale modeling of Mitochondrial Cristae Structure on Metabolic Function

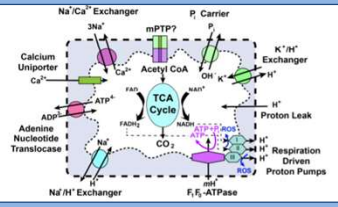
Nasrin Afzal[1,], Kavya Parekh[2], Bindu Srinivasa[2], Zheng Liu[3], Carmen Mannella[3,4], W. Jonathan Lederer[4], and M. Saleet Jafri[1,4]*

[1]Krasnow Institute for Advanced Study and School of Systems Biology, George Mason University, Fairfax VA 22030,
[2]Thomas Jefferson High School for Science and Technology, Alexandria VA 22312,
[3]Wadsworth Center, New York State Department of Health, Albany NY 12201,
[4]Center for Biomedical Engineering and Technology, University of Maryland School of Medicine, Baltimore MD 21201

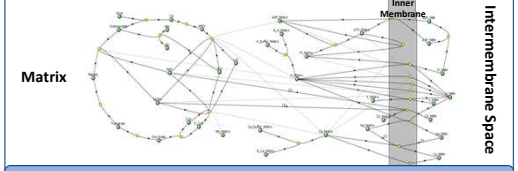
Abstract

The mitochondrial cristae structure is thought to play a significant role in mitochondrial function and energy metabolism. Our integrated multiscale modeling and experimental studies seek to develop a fundamental understanding of the interplay of the mitochondrial cristae organization and mitochondrial metabolic function. Our previously published model (Nguyen et al., 2007) for mitochondrial energy metabolism was integrated and upgraded to take account of our new data on both activity-dependent regulation of ATP production and new information on cristae structure. This spatiotemporal model of the mitochondrion was developed using the Virtual Cell platform in a two-dimension representation. The studies examine the effect of geometry and shape of the cristae on metabolic function and specifically ATP production and ionic concentrations. The model predicts spatial gradients of ion and metabolite concentrations within the mitochondrial matrix and within the intermembrane space. The existence of these gradients affect mitochondrial fluxes across the inner membrane. ATP production is also affected. The model suggests that changes to mitochondrial cristae geometry alters the gradients of ion and metabolite concentrations. Simulations also suggest that heterogeneous placement of the energy metabolism machinery can alter function. These results suggest that metabolic modeling (extended to 3D structures) can be useful for identifying structural features of mitochondria that influence function in multi-scale investigations.

Multiscale Modeling and Method

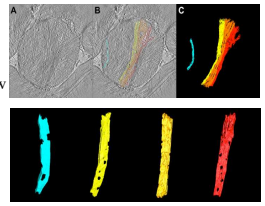


Virtual Cell BioModel



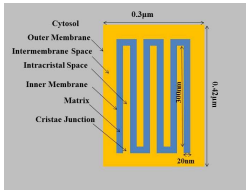
3D Mitochondrial Structure

Slice through electron tomogram of typical cardiac muscle mitochondrion (A) with select cristae traced (B-C) and surfaces rendered (below). Cristae are predominantly lamellar with narrow junctions to peripheral inner membrane, and contain numerous fenestrations tens of nm wide. We are collecting numerous tomograms of cardiac muscle mitochondria to establish the geometry of the inner membrane cristae in different states.



2D Simulation

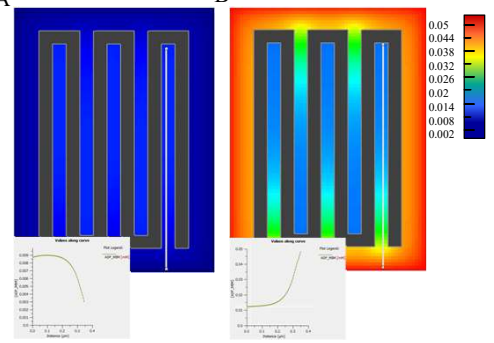
First phase studies of mitochondria are done in 2D using the following structure model with constant concentration of species on outer membrane of mitochondria as boundary conditions. Simulations presented are for 1ms, by which time the system is at or near stationary state.



Results

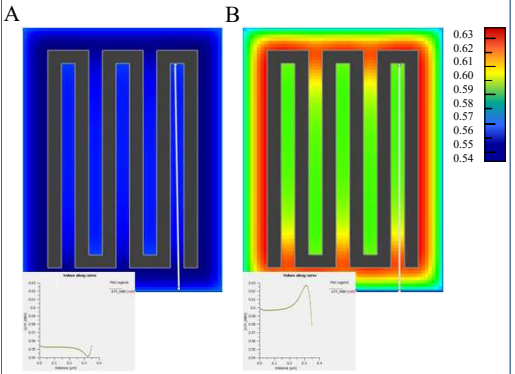
A: Mitochondrial Metabolic State

Intracristal/intermembrane [ADP] gradient with boundary (cytosolic) [ADP] of A) 0.002 mM and B) 0.05 mM (Plots show values along white lines):



$[ADP]_{CRISTA} > [ADP]_{IMS} = [ADP]_{CYTOSOL}$ $[ADP]_{CRISTA} < [ADP]_{IMS} = [ADP]_{CYTOSOL}$

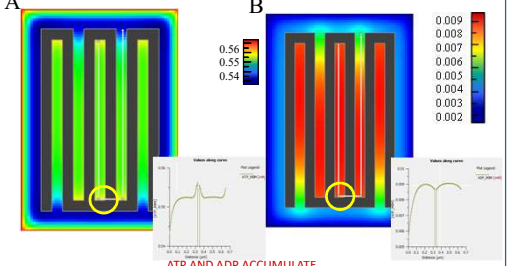
Intracristal/intermembrane [ATP] gradient with boundary (cytosolic) [ATP] = 0.56 mM and [ADP]= A) 0.002 mM and B) 0.05 mM,



$[ATP]_{CRISTA} > [ATP]_{IMS} < [ATP]_{CYTOSOL}$ $[ATP]_{CRISTA} < [ATP]_{IMS} > [ATP]_{CYTOSOL}$

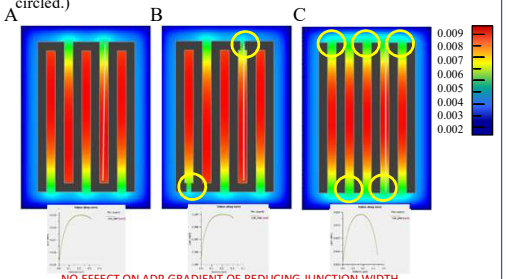
B: Cristae Geometry and Mitochondrial Metabolic State

Three variations in 2D crista geometry were used: (1) no junctions **(detached cristae),** (2) junctions at both ends of crista **(open cristae)**, and (3) narrow (10 nm) junctions **(restricted cristae)**. Here are results for intracristal [ATP] and [ADP] in a model with a detached (yellow circle) crista for boundary [ADP] = 0.002 mM:



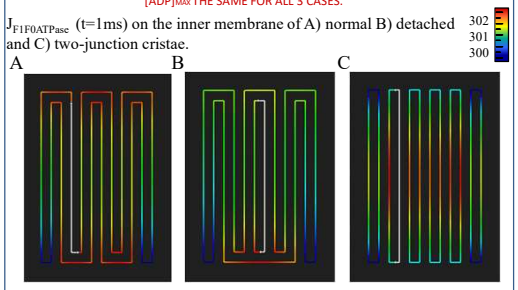
ATP AND ADP ACCUMULATE
IN DETACHED CRISTAE AT LEVELS EQUAL TO MAX IN CRISTAE WITH JUNCTIONS

ADP gradients inside cristae with A) normal junctions, B) restricted junctions (yellow circle), and C) two junctions. (Unusual junctions circled.)



NO EFFECT ON ADP GRADIENT OF REDUCING JUNCTION WIDTH.
LARGE CHANGE IN ADP GRADIENT FOR 2 JUNCTIONS / CRISTA.
$[ADP]_{MAX}$ THE SAME FOR ALL 3 CASES.

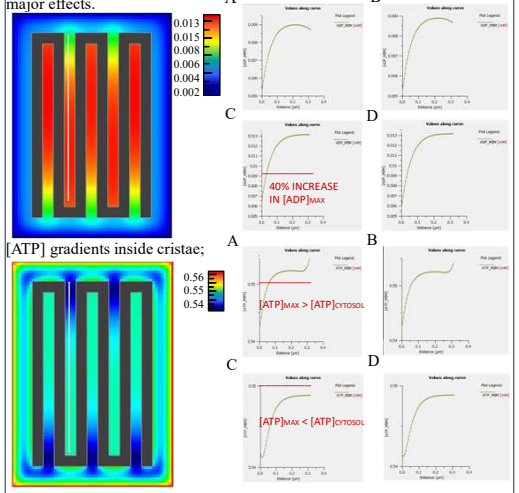
$J_{F1F0ATPase}$ (t=1ms) on the inner membrane of A) normal B) detached and C) two-junction cristae.



DIFFERENCES IN RATE OF ATP PRODUCTION ARE SMALL
ATP PRODUCTION GENERALLY HAS POSITIVE CORRELATION WITH INTRACRISTAL [ADP]
ESPECIALLY FOR CRISTAE OPEN AT BOTH ENDS (C)

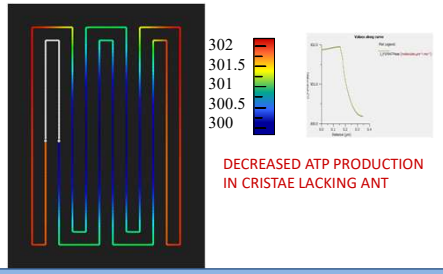
C: Non-homogeneously Distributed Membrane Proteins

[ADP] in cristae with A) Homogenous protein distributions, B) F_1F_0ATPase only on cristae, C) ANT only at periphery D) Both B and C (In all cases total protein is conserved). In 2D simulations conditions C and D have major effects.



[ATP] gradients inside cristae;

Flux of F_1F_0ATPase for ANT only on peripheral region of inner membrane (not inside cristae)



DECREASED ATP PRODUCTION
IN CRISTAE LACKING ANT

Conclusion

1. Under conditions of these simulations, ADP gradients occur in cristae.
2. ADP gradients are affected by number of junctions per crista and by distribution of ADP/ATP translocase(ANT) but not ATP synthase.
3. ANT localization in cristae may be important for maximum efficiency of ATP production.

Acknowledgments

This work is supported in part by U01HL116321.
Virtual Cell platform is supported by grant # P41 GM103313.